PROCESS FOR AUGMENTING CONNECTIVE MAMMALIAN TISSUE WITH IN SITU POLYMERIZABLE NATIVE COLLAGEN SOLUTION

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention is a method of augmenting or replacing connective tissue in a living mammal by implanting a solution of a natural tissue material which polymerizes upon implantation into a fibrous mass of tissue which is non-reactive, stable, resistant to secondary infection and has the potential for vascularization. Specifically, the invention resides in the use of a solution of solubilized, purified, native, in situ polymerizable collagen as the material which is implanted.

2. Brief Description of the Prior Art

Collagen is a natural material which serves as supporting tissue in many living systems. It is a principal component of skin, tendon, cartilage, bone and interstitium.

The molecular structure of collagen has been studied and documented. Collagen is characterized as a fibrous protein made up of helixes of three polypeptide chains having biologically important end regions. Collagen may be modified by treatment with proteolytic enzymes to solubilize it and lower its antigenicity[1]. It is reported that after such treatment collagen fibers tend to precipitate with increasing pH, increasing ionic strengh and increasing temperature.

[1]Gross, J., Highberger, J.H., and Schmitt, F.O., *Proc. Nat. Acad. Sci.* (US) 40:679, 1954.

Many uses of enzyme-solubilized collagen (ESC) as a biomaterial have been investigated or suggested[2,3,4]. For instance collagen gel formed by irradiating or ascorbic acid-treating ESC to prevent fiber precipitation has been used as a vitreous replacement in the eye. Also films of irradiation-crosslinked ESC have been used as corneal replacements, dialysis membranes, heart valve prostheses, vessel prostheses, burn coverings and surgical hemostasis (as a film or powder).

[2]"Collagen as a Biomaterial", Rubin, A. L. and Stenzel, K. H., Departments of Surgery and Biochemistry, Cornell University Medical College (New York).

[3]"Collagen: Medical and Surgical Applications", Rubin, A. L., Miyata, T., and Stenzel, K. H., Departments of Surgery and Biochemistry, New York Hospital-Cornell Medical Center (New York).

[4]"Medical and Surgical Applications of Collagen", Chvapil, M., Kronenthal, R., and van Winkle, W., *International Review of Connective Tissue Research*, Vol 6, pp 1–61, 1973.

Collagen has not been used previously to augment soft tissue. Prior soft tissue augmentations have involved autografts and homografts of bone, cartilage or dermis, insertion of alloplastic implants, or injection of alloplastic materials such as liquid silicone. Bone and cartilage may fill a soft tissue defect, but unless the depressed area is due to a deficiency of underlying bony framework, the lack of pliability in the augmented area will be unsatisfactory. The surgical technique of inserting bone, cartilage or dermis often involves wide undermining of soft tissue and the creation of a substantial, and sometimes additional, recipient site scar. There is also a tendency for such grafts to undergo resorption which often cannot be predicted accurately. Moreover, fine contouring of multiple small areas is often extremely difficult with such grafts. The donor sites for obtaining bone and cartilage autografts are rather limited and a noticeable scar is often created.

The donor site problems are not existent with the use of homograft material. The homograft dermis is unsuitable because it is always rejected. Rejection may be less of a problem with bone and cartilage homografts, but is unpredictable[5].

The *Transplantation of Tissues*, Peer, L., Williams & Wilkins Co, Baltimore, 1959. 1959.

Solid silicone implants require that the recipient site be undermined, result in a scar at the insertion site, have a significant tendency to drift, cause seromas, become surrounded by hard fibrous tissue and occasionally become infected or erode through the overlying soft tissue. Some of these problems are shared by the injectable silicone liquids.

SUMMARY OF THE INVENTION

The invention resides in the discovery that solubilized collagen is a readily available, biologically acceptable material which may be implanted as a solution and which, upon implantation, condenses at the implantation site into non-reactive, stable tissue which is rapidly colonized by host cells and vascularized. Specifically the invention is a method of augmenting connective tissue in a living mammal comprising implanting or applying a solution of solubilized, purified, native, in situ polymerizable collagen into or onto the mammal, as the case may be, at the augmentation site which polymerizes at the site into fibrous tissue. As used in the claims the term "administering" includes the acts of implanting and applying the solution.

Since the method employs collagen in a solution implantation may be effected by conventional injection techniques rather than surgical implantation. Thus the method avoids the undermining of body tissues and scarring associated with solid alloplastic implants. It may also be used for fine contouring small, irregular tissue defects. More importantly once the material is implanted it polymerizes into fibrous tissue possessing all the attributes of an ideal prosthesis, namely, (a) its texture is compatible with the existing tissue at the site, (b) it is non-toxic, (c) it is non-reactive (ie, it has low antigenicity), (d) it is stable in the sense that the net amount of tissue remains constant, (e) it is colonized by host cells and is vascularized so that it is resistant to subsequent infection and (f) no immunosuppressive drugs need be administered.

DETAILED DESCRIPTION OF THE INVENTION

The collagen used in the invention method may be collected from any number of mammalian sources. Homograft, autograft and xenograft sources have been used successfully.

The tissue is prepared for treatment by shaving it (if it is animal skin), and removing any loose connective tissue and residual fat. It is then cut into small pieces, dessicated and milled to a powder.

The collagen may be solubilized from the tissue without denaturation (eg, digestion with proteolytic enzymes, salt or acid extraction, or extraction with active amines such as cysteamine and penicillamine) or with denaturation followed by renaturation (eg, heating or treatment with strong acids, detergents or other denaturing chemicals followed by renaturation such as by prolonged incubation at controlled temperatures against acid or neutral low salt neutral solutions). Because the latter procedure is more complex and time-consuming, solubilization without denaturation is pre-